REMARKS

Claims 23-43 are pending in this application. All the pending claims stand rejected for obviousness under 35 U.S.C. §103(a). In addition, claim 27 has been rejected for indefiniteness under 35 U.S.C. §112, second paragraph. This Reply amends claims 23, 24, 26, 27, 30, 31, and 38-40; cancels claims 28, 29, 32-34, 36, 41 and 42; and adds new claims 43-49. Applicant requests reconsideration of the Application in view of the above amendments and the following remarks, which address each of the rejections set forth in the Office Action.

Claim Amendments

In claims 23, 31, and 40, the feature "*connective tissue cells or progenitor cells*" has been replaced by "*chondrogenic cells*." The two types of chondrogenic cells, namely "*chondrocytes*" and "*chondrocyte precursor cells*" are recited in dependent claim 30, and new dependent claims 43 to 49. Support for "*chondrogenic cells*," "*chondrocytes*," and "*chondrocyte precursor cells*" is found, for example, on page 9, lines 21 to 26, of the specification:

> *Thus a particular aspect of the invention relates to the use of polysulphated alginate in a matrix for osteochondral cells, more particularly* ***chondrogenic cells****, i.e. cells which are capable of producing cartilage or cells which themselves differentiate into cells producing cartilage, including* ***chondrocytes*** *and cells which themselves differentiate into chondrocytes (i.e.* ***chondrocyte precursor cells).*** [emphasis added]

Claims 26 and 27 have been amended to clarify the dependency of claim 27. Claim 27 has been further amended to modify the claimed ratio to be "between 1:1000 and 1:10,000." Support for this change is found in Example 3 on page 15, which refers to a 100 ml composition with 100 µg sulphated alginate (i.e. a matrix comprising 1 µg/ml polysulphated alginate, according to claim 23) . The composition further comprises 1 gram non-sulphated alginates. Accordingly the polysulphated alginate and the unsulphated alginate are present in a weight ratio of 1:10,000. For a matrix comprising 10 µg/ml polysulphated alginate, this ratio becomes 1:1000.

The features of former claims 29, 33 and 42 have been incorporated in the independent claims.

Claim 38 has been amended by specifying the matrix "*according to claim 31*."

Claim 39 has been amended by specifying osteochondral defects as cartilage defects. This amendment is supported in the application, for example, on page 10, lines 21 to 24:

> *Osteochondral defects in the context of the present invention should also be understood to comprise those conditions where repair of* ***cartilage*** *and/or bone is required in the context of surgery such as, but not limited to, cosmetic surgery (e.g. nose, ear).*

No new matter is added by any of these amendments.

Rejections under 35 U.S.C. §112

Claim 27 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. In particular, the Office Action asserts that there is a lack of antecedent basis in claim 27 for the term "unsulphated alginate" since that term is not recited in the base claim (i.e. claim 23). With this Reply, Applicants have amended claim 27 so that it now depends from claim 26, which does recite the term "unsulphated alignate." Thus, the present amendment of claim 27 obviates the §112 rejection. This rejection may now be withdrawn.

Rejections under 35 U.S.C. §103

Claims 23-42 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kavalkovich et al. (In vitro Cell. Dev. Biol. – Animal, 2002, Vol. 38, p. 457-466) in view of Ronghua et al. (Carbohydrate Polymers, April 2003, Vol. 52, p. 19-24) and further in view of Kawada et al. (Arch. Dermatol. Res., 1999, Vol. 291, p. 542-547) and further in view of Rihova (Advanced Drug Delivery Reviews, 1996, Vol. 21, p. 157-176). Applicants respectfully traverse this rejection as applied to the amended version of the claims.

The claims of the present application have been amended to recite matrices comprising minute amounts of polysulphated alginates (1 to 10 μg/ml), and to recite products comprising chondrogenic cells or methods applicable to chondrogenic cells. It

has been found in the present invention that within a narrow range, small amounts of polysulphated alginate stimulate the metabolism of chondrogenic cells. This results in an enhanced matrix synthesis. As illustrated in the first column of Table 1, on page 15, of the present specification, once the concentration reaches 100 μg/ml polysulphated alginates have no longer have an additional effect on cell-associated matrix synthesis.

Kavalkovich *et al.* describe the cultivation of human mesenchymal stem cells, considered by these authors as an attractive source of chondrocyte cells. The Examiner recognizes the difference between the pending claims of the present invention and Kavalkovich *et al.*, in that Kavalkovich *et al.* do not teach polysulphated alginate. The parameters which are investigated in Kavalkovich are cell density and addition of hyaluronic acid.

The Examiner states that the skilled person would be motivated by Ronghua *et al.* to consider alginate sulfates for their anti-coagulant activity to obtain a biocompatible (i.e. non-thrombogenic) matrix. However Rhongua *et al.* states in the introduction on page 19, left column, second paragraph, lines 1-2, that:

> *"the blood- or tissue compatibility of sodium alginate was not able to meet the requirement in **some cases**" [emphasis added]*

This passage teaches that the incompatibility of sodium alginate is an unusual phenomenon. Accordingly a skilled person would not automatically consider the inclusion of sulfated alginates in a matrix. Indeed, the fear of an eventual blot clotting on an implant may be of relevance, for example, for artificial blood vessels or microspheres

which are transported in the blood stream, where blood clot formation may have dramatic consequences. However, for the implantation of matrices with cartilage forming cells, there are no detrimental effects of an eventual blood clot formation around the implant. Accordingly there is no reason for the skilled person envisaging cartilage implantation to consider the inclusion of anti-coagulants at all.

In addition, the effective concentration range of 10 to 100 µg/ml polysulfated alginate, shown in figure 3 of Rhongua, differs an order of magnitude from the currently claimed range of 1 to 10 µg/ml. Whereas paragraph 3.2.1. refers to values of 17 µg per ml, much stronger anticoagulant effects are obtained with values of 66/µl. If any optimization would be considered by the skilled person, it would be to explore the high concentration range rather than investigating concentrations below 10 µg/ml. Inclusion of sulfate alginates in accordance with the teaching of Rongua would thus have led a skilled artisan to investigate concentrations closer to 100 µg/ml, which would not have resulted in an enhanced extracellular matrix synthesis as obtained by the present invention.

With respect to Kawada *et al.* on the growth of endothelial cells using sodium alginate, without sulfate (see first paragraph of material and methods), the Examiner indicates that the skilled person would be motivated to use unsulfated alginate because he/she "*would have realized that stimulation of endothelial cells and proliferation were necessary for vascularization of the implant.*"

It is noted that the claims of the present invention have been amended to recite chondrogenic cells, i.e. cells forming cartilage, and to specify the concentration of sulfated alginates that affects extracellular matrix organization. It is furthermore noted that high quality cartilage is hyaline and non-vascularized. Vascularization of cartilage is not desired at all. For this reason, it is submitted that prior art on unsulphated alginates that is unrelated to cartilage and encourages vascularization is of no relevance at all for the present claims related to sulfated alginates in the context of cartilage formation.

For the reasons provided above, Applicant respectfully submits that the claims are patentable over the cited references, and the §103 rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the Application is now in condition for allowance and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for three (3) months, to and including December 3, 2009.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: _____

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